

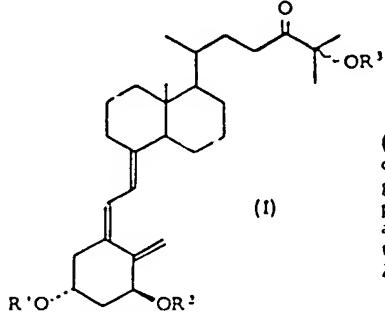
50771 D/28
TEIJIN KK

B05 (B01)

TEIJ 26.10.79
*JS 6061-351

26.10.79-JP-137771 (26.05.81) A61k-31/59 C07c-172
1-Alpha, 25-di:hydroxy-24-oxo:cholecalciferol derivs - exhibit vitamin/D₃ pharmacological activities. prep'd. from 24-oxo-cholesta-5,7-diene cpds.

1a,25-Dihydroxy-24-oxocholecalciferols of formula (I) are new:



(R', R² and R³ = H or hydroxy protecting gp. (pref. 1-12C aliphatic or aromatic acyl, trialkylsilyl, 2-tetrahydropyranyl, or 2-tetrahydrofuranyl)).

B(1-D2, 3-G). 2

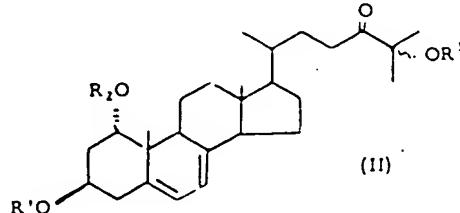
109

USE/ADVANTAGE

(I) exhibit vitamin D₃-like pharmacological activities. On reduction of the 24-oxo, (I) are converted into 1a, 24, 25-trihydroxyvitamin D₃ as active vitamin D₃.

PREPARATION

(I) are prep'd. by irradiating 1a,25-dihydroxy-24-oxo-cholesta-5,7-dienes (II) with ultraviolet rays to yield 1a,25-dihydroxy-24-oxoprevitamins D₃, isomerising the latter with thermal energy, if required followed by removal of the hydroxy protecting gp.



J56061351+

The UV rays pref. have wavelength 200-360 nm, esp. 260-310 nm. The reaction is conducted in an inert solvent - including hydrocarbons and halohydrocarbons (e.g. hexane, heptane, PhH, PhMe, xylene, PhCl), ethers (e.g. Et₂O, THF, dioxane), and alcohols (e.g. MeOH, EtOH, PrOH) at a temp. of -20°C to 120°C, pref. -10°C to 50°C. The subsequent thermal isomerisation is carried out at 20-120°C, pref. 40-100°C in the inert solvent.

EXAMPLE

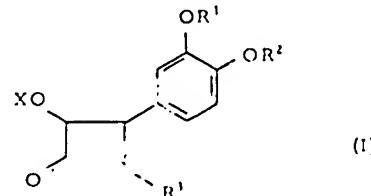
A soln. of 70 mg 1a,3β,25-trihydroxy-24-oxocholesta-5,7-diene dissolved in a mixt. of 50 mg deoxygenated EtOH and 500 ml Et₂O was irradiated with a 200W lamp surrounded by a Vycor filter at 10-20°C with stirring for 6 hrs. The cold soln. was evapd. in v_u. uo at 30°C, and the residue was dissolved in 250 ml deoxygenated PhH and refluxed under heating for 2.5 hr. After the reaction completion, the mixt. was evapd. in vacuo, and the resulting residue was chromatographed on a thin layer of silica gel preliminarily treated with 2% AgNO₃-MeCN (solvent:CHCl₃-MeOH) and of silica gel (PhH-Me₂CO) to give 10.8 mg 1a,25-dihydroxy-24-oxovitamin D₃, mp. 91-93.5°C. (6ppW52)

J56061351

50772 D/28
SAGAMI CHEM RES CENTREB03
SAGA 24.10.79
*JS 6061-352

24.10.79-JP-135485 (26.05.81) C07c-101/77 C07d-205/08
3-Hydroxy-β-lactam cpds. can be prep'd. economically - and are used in DOPA prep'n. used in antiparkinson treatment.

3-Hydroxy-β-lactam cpds. of formula (I) are new:



(R¹ and R² = H, lower alkyl, benzyl or acyl, or R¹ and R² taken together may form alkylene;

R¹ = alkyl, aryl or heteroaromatic gp.;

X = H, benzyl or tosyl).

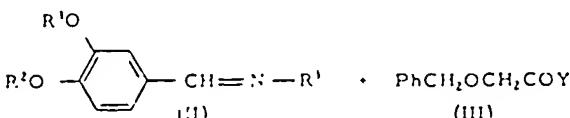
USE/ADVANTAGE

(I) can be converted into DOPA (useful as antiparkinson-

B(6-A2, 7-D1). 2

110

ism agent) on reaction with NaN₃, cleavage of the β-lactam ring, and acid treatment. (I) can be prep'd. from cheap raw material.

PREPARATION

Step (A) → (I) (X = benzyl) → (I) (X = H) → (I) (X = tosyl)
(Y is not defined but probably halogen).

Step (A) is carried out in a solvent, e.g. PhH, PhMe, THF, CH₂Cl₂, in presence of a tert. amine, e.g. Et₃N, Pr₃N, Bu₃N, pyridine, N-methylpiperidine, N-methylpyrrolidine DBU, at -78°C to 100°C.

J56061352+

Step (B) comprises hydrogenolysis with Pd catalyst (e.g. Pd black, Pd-C) in a solvent (e.g. MeOH, EtOH, CH₂Cl₂, CHCl₃, PhH, PhMe, THF, MeCN, DMF) at room temp. to 150°C, pref. 50-100°C.

Step (C) comprises tosylation with p-TsCl in presence of a tert-amine in an aprotic solvent (e.g. CH₂Cl₂, CHCl₃, PhH, PhMe, THF, MeCN, Me₂CO, DMF, DMSO) at -30°C to 100°C.

EXAMPLE

I. a soln. of 5.00 g 3,4-dimethoxybenzylideneaniline and 2.50 g Et₃N in 50 ml PhH was dropwise added slowly a soln. of 4.60 g benzyloxyacetyl chloride in 50 ml PhH under ice cooling. The reaction mixt. was gradually warmed up to room temp., stirred for 15 hrs., washed with water, dried on MgSO₄, and evapd. in vacuo to give 8.18 g light yellow oil. This was chromatographed on silica gel and eluted with n-hexane-EtOAc (4 : 1) to give 4.16 g cis-isomer of 1-phenyl-3-benzyloxy-4-(3,4-dimethoxyphenyl)azetidin-2-one as white crystals, m. pt. 130-133°C, and 2.38 g trans-isomer as a colourless oil, n_D^{25.0} : 1.6018. (1OppW52).

J55061152

50774 D/28

B03 C02 E13

MI: TU 23.10.79

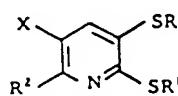
*J56061-354

MITSUBISHI CHEM IND KK

23.10.79-JP-136740 (26.05.81) C07d-211/90 C07d-213/80

Nicotinic acid derivs. - used as agrochemicals, drugs and chemical intermediates

Nicotinic acid derivs. of formula (I) are new:



(I)

(R¹ = lower alkyl (e.g. Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, s-Bu, t-Bu); R² = H, lower alkyl or aryl (e.g. phenyl, tolyl); X = lower alkoxy carbonyl (e.g. MeOCO-, EtOCO-, n-PrOCO-, i-PrOCO-) or COOH).

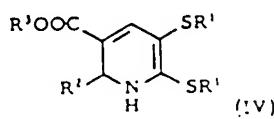
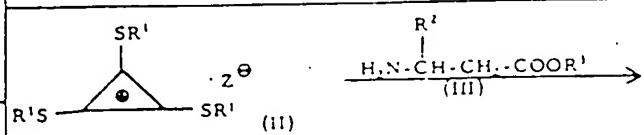
USE

(I) are utilized as agrochemicals or drugs or as raw material in production of various chemicals. (I) can be converted into nicotinic acid or its esters by removal of -SR¹ on hydrogenolysis with Raney Ni catalyst.

PREPARATION

BC(7-D4) E(7-D4) N(S-A). 1

1 1 1

-H₂ → (I)

(Z⁻ = anion (e.g. halogen ion, ClO₄⁻, BF₄⁻, SbF₆⁻, SbCl₆⁻, AlCl₄⁻); R¹ = lower alkyl).

DETAILS

(II) has been described in J48096564.

The reaction is carried out in a solvent, e.g. CH₂Cl₂, CHCl₃, dimethoxyethane, DMF, MeOH, pref. in presence of a base, e.g. NaH, t-BuOK, at -100°C to the reflux temp. of a

J56061354.

the solvent used, pref. room temp. to 100°C, for a period of 0.1-10 hrs., pref. 0.5-5 hrs.

The subsequent dehydration is achieved by allowing (IV) to stand in a halogenohydrocarbon solvent, e.g. CHCl₃, CCl₄, fluorohydrocarbon, perfluorohydrocarbon, at 0°C to the reflux temp. of the solvent used, pref. room temp., for a period of 3-24 hrs., pref. 10-15 hrs.

EXAMPLE

A mixt. of tri-t-butylthiocyclohexenonium perchlorate (1 mmole, 403 mg.) and methyl α -aminopropionate (2 mmole) in 40 ml. DMF is allowed to stand at 80°C in presence of NaH (3 mmole) for 1 hr. Water is added, and the mixt. is extracted with *t*-xane. The extract is dried on Na₂SO₄ and evapd., the residue is chromatographed on silica gel to give methyl 2,3-di-t-butylthio-1,6-dihydronicotinate in 72% yield.

This is dissolved in 10 : 1 *t*-BuOC₂ and allowed to stand under air for 2^{1/2} hrs. to give methyl 2,3-di-t-butylthio-nicotinate in quantitative yield. (1OppW52)

J56061354